AMENDMENTS TO THE DRAWINGS

Submitted herewith please find (1) sheet of replacement drawings in compliance with 37 C.F.R. § 1.84. The Examiner is respectfully requested to acknowledge receipt of these drawings.

The submitted drawing is intended to replace the drawings previously submitted.

Attachment: Replacement Sheet: One (1)

REMARKS

This Amendment, filed in reply to the Office Action dated June 15, 2010, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

As of the Non-Final Office Action dated June 15, 2010, claims 1, 6-21, 24-27, 29-30 and 32-35 are pending in the application. Claims 17-21, 24-27, 30 and 32-34 are withdrawn from consideration and claims 1, 6-16, 29 and 35 are rejected.

With this response, claims 1, 10 and 35 are currently amended. Claims 6-8, 11-16 and 29 are as originally presented. Claim 36 is new.

Support for the claim amendments can be found throughout the specification as filed including the original claims.

Specifically, support for "administering to a human" in claims 1 and 35 can be found on page 27, lines 1-4, which states:

> ". . . (2R)-2-propyloctanoic acid or a salt thereof has markedly low toxicity and can be judged sufficiently safe so far as it is used in mammals, particularly humans, by the method and dosage of the present invention."

Support for the administration of (2R)-2-propyloctanoic acid "for about 0.5 to about 3 hours once a day" and a period of time of "1 hour" in claims 1, 35 and 36 can be found on page 22, lines 21-24, which states:

> ". . . it is desirable to carry out the continuous administration, for example, over an about 0.5 to about 3 hour period of time, preferably about 0.5 to about 1.5 hours, particularly preferably about 1 hour."

Support for "a period of treatment lasting from 1 to 100 days" in claim 1 can be found in original claim 9 that recites:

> 9. The method according to claim 1, wherein the dose of parenteral administration per once a day during an administration

period of 1 day to 100 days is within a range of about 100 mg to about 2,000 mg.

Entry and consideration of this amendment are respectfully requested.

Drawings

The drawings are objected to because they fail to show the difference between the "3-4" group and the "5" group in the Glasgow Outcome Scale as described in the specification.

As requested by the Examiner, Applicants have amended the depiction of group "5" in FIG. 2. Group "5" is now shown as filled in black. The amendment therefore shows the difference between the "3-4" group and the "5" group as required by 37 C.F.R. 1.83(a).

Accordingly, Applicants request the objection to the Drawings be withdrawn and that Figures 1 and 2 in the present Application be replaced with the attached replacement sheet.

Claim to Priority

Applicants thank the Examiner for acknowledging Applicants' claim to foreign priority, and for acknowledging receipt of a certified copy of Applicants' foreign priority document, namely JP 2004-174577.

Information Disclosure Statement

Applicants also thank the Examiner for returning signed and initialed copies of the PTO Forms SB/08 that accompanied the Information Disclosure Statement filed on February 12, 2008.

Claim Rejections under 35 U.S.C. § 103(a) - the Tateishi reference

Claims 1, 6, 7, 9-16, 29 and 35 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Tateishi et al. (Journal of Cerebral Blood Flow & Metabolism, June 2002, vol. 22,

no. 6, pp. 723-734).

Using a permanent middle cerebral artery occlusion (pMCAO) model in rats, Tateishi et al. allegedly shows that there is a significant increase in the infarct volume between 24 and 168 hours after pMCAO, which closely resembles the time course of infarct expansion in human stroke. The Examiner contends Tateishi et al. teaches administration of (2R)-2-propyloctanoic acid (ONO-2506) to pMCAO treated rats leads to mitigation of delayed infarct expansion, early improvement of neurologic deficits and a reduction in the expression of S-100β.

Tateishi et al. allegedly reports that rats administered intravenously with 1mg/kg, 3 mg/kg or 10 mg/kg daily (2R)-2-propyloctanoic acid showed a significant reduction in the infarct volume at 168 hours. The Examiner maintains a continuous intravenous administration for 7 days of 10 mg/kg daily ONO-2506 equates to 700 mg for a human with an average weight of 70 kg. The Examiner then alleges that even if Tateishi et al. does not specifically teach the range of between about 100 mg to about 2,100 mg of (2R)-2-propyloctanoic acid, the Examiner asserts one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Tateishi et al. and the claimed range amounts because Tateishi et al. teaches the administration of (2R)-2-propyloctanoic acid (ONO-2506) to a rat intravenously 10 mg/kg daily significantly reduced the infarct volume at 168 hours. Thus, if one were to administer the same compound at 10 mg/kg to a human at 70 kg, one would administer 700 mg, which is within the range of the claimed invention.

Applicants respectfully traverse the rejection by asserting the Office failed to establish a *prima facie* case of obviousness.

In determining obviousness, the law requires an analysis of the underlying factual inquiries including,

(1) determining the scope and content of the prior art;

(2) ascertaining the differences between the claimed invention and the prior art; and

(3) resolving the level of ordinary skill in the pertinent art.[2]

In the wake of the decision by the Supreme Court in *KSR International Co. v. Teleflex Inc.*[3], the Office also established Guidelines[4] that should be followed in making an obviousness determination. The Guidelines indicate a rationale must be set forth as to why the claimed invention is obvious. The Guidelines indicate the following rationales are indicative of obviousness:

(a) combining prior art elements according to known methods to yield predictable results;

(b) simple substitution of one known element for another to obtain predictable results;

(c) use of a known technique to improve similar devices (methods, or products) in the same way;

(d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(e) "Obvious to try"—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(f) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

[2] *Graham v. John Deere Co.* 383 US 1, 148 USPQ 459 (1966).
[3] *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398, 82 USPQ2d 1385 (2007)
[4] MPEP § 2141 and Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v.Teleflex Federal Register / Vol. 75, No. 169 / September 1, 2010

(g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Thus, according to the Guidelines, **predictability** is a key determinant in an obviousness analysis, particularly in an unpredictable art such as biotechnology.

Applicants have the following comments:

Applicant's effective dosage of (2R)-2-propyloctanoic acid is distinct from that taught by the Tateishi reference

The Examiner points out that if the dosage of 10 mg/kg taught by the Tateishi reference, is administered to a human of body weight of 70 kg, the total dosage administered equates to 700 mg per day, a value that allegedly is also taught by Applicant's disclosure. Applicants respectfully disagree.

Applicants assert the Examiner's reasoning that dosages of (2R)-2-propyloctanoic acid administered to rats can be extrapolated to humans based purely on weight is flawed. Applicants point out the efficacy of any pharmaceutical agent must also take into account the kinetics of drug administration. In the example given by the Examiner, the dosage per hour equates to 700 mg/ 24h = 29,17 mg/h and for a 70 kg human, the effective dosage is 29,17 mg/h ÷ 70 kg = **0.42 mg/kg/h**.

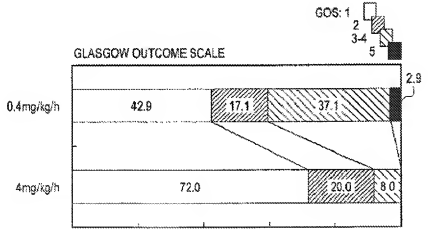
The specification on page 22, lines 25-31 and on page 23, lines 1-4, however states:

> "Regarding a desirable method according to the present invention for parenterally administering from about 100 mg to about 2,000 mg per dose of (2R)-2-propyloctanoic acid or a salt thereof for the treatment of a neurodegenerative disease, a neuropathy or a disease whose treatment requires neural regeneration, its examples include a method in which (2R)-2-propyloctanoic acid or a salt thereof is continuously administered into a vein spending **about 1 hour once a day** using an infusion bag or the like, at **a dose of about 2 mg to**

> **about 12 mg per 1 kg of body weight** of each patient during a drug administration period of 1 day to 100 days." (Emphasis added)

Hence, even if the teachings of the Tateishi reference are extrapolated to humans, which is far from being guaranteed success (see below), the dosage rate of 0.42 mg/kg/h (2R)-2-propyloctanoic acid **falls outside** the range recited in the specification, i.e. about 2 to 12 mg/kg/hr.

Applicants also contend the Tateishi dosage is largely ineffective at preventing death from cerebral ischemia. In Figure 2 (reproduced below), significant death (Glasgow Outcome Scale (GOS) = 5) is eliminated by treatment with 4 mg/kg/h (2R)-2-propyloctanoic acid, whereas death occurs in the group of patients treated with 0.4 mg/kg/h, a dose equivalent to the dosage reported in the Tateishi reference.



Applicants therefore contend a person of ordinary skill in the art at the time of filing of the Application would know that the 24 hour administration of a pharmaceutical agent at the Tateishi rate of 0.42 mg/kg/h would be insufficient to treat cerebral ischemia because the dose of (2R)-2-propyloctanoic acid in the bloodstream would not reach a sufficient concentration to be effective.

Applicant's invention teaches the administration of high dose (2R)-2-propyloctanoic acid for period of time lasting only about 3 hours or less

A key feature of the present invention is the administration of high dose (100 mg to 2000 mg) (2R)-2-propyloctanoic acid over a short period of time, lasting about 0.5 to 3 hours, for the treatment of cerebral infarction with almost no side effects.

Contrary to the teachings of Applicant's invention, the Tateishi reference discloses the administration of (2R)-2-propyloctanoic acid in a rat pMCAO model over a period of time of 24 hours, not the 0.5 to 3 hours as required by currently amended claim 1 or the 1 hour as required by currently amended claim 35.

Applicants therefore assert it would not have been obvious to a person of ordinary skill at the time of filing of Applicant's invention that high dose administration of (2R)-2-propyloctanoic acid for period of time lasting 3 hours or less could be effective in treating cerebral ischemia without causing any adverse side effects, as demonstrated in Examples 1 and 2 of the specification as filed.

Efficacy and tolerance of high dose (2R)-2-propyloctanoic acid in humans is unpredictable

The Tateishi reference teaches administration of (2R)-2-propyloctanoic acid ***to rats not humans***. Applicants argue the results in rats are not necessarily applicable to humans. The pharmacokinetics of a drug in humans depends on several factors other than initial dose including, for example, absorption, bioavailability, distribution, renal clearance, metabolic clearance and biologic half-life.

In this regard, the Merck Manual states:

> "Regardless of how a drug effect occurs—through binding or chemical interaction—the concentration of the drug at the site of action controls the effect. ***However, response to concentration may be complex and is often non linear***. The relationship between the drug dose, regardless of route used, and the drug concentration at the cellular level is even more complex." (Emphasis added)

Non-linearity infers the biological response is unpredictable and not solely attributable to the dose administered. The cytotoxicity of the drug in humans is also highly unpredictable. A person of ordinary skill would expect cytotoxicity in humans to increase with the dose. Ultimately the only way to determine a drug's toxicity and side effects in humans is to perform Phase I clinical trials, which are mandated by the FDA precisely to determine tolerance to side effects.

Applicants assert a person of ordinary skill administering (2R)-2-propyloctanoic acid in humans would be inclined ***not*** to increase dosage of the drug for fear it would trigger adverse side effects, especially as the Tateishi reference teaches an optimal human equivalent dose of 97 mg/kg weight. Certainly, nothing in the Tateishi reference would inspire a person of ordinary skill to test the drug in humans at dosages 10 or 20 times higher than previously reported, i.e. doses as high as 2100 mg/kg.

The inventor's finding that high dose (2R)-2-propyloctanoic acid is very well tolerated in humans is therefore surprising and unexpected.

Claim Rejections under 35 U.S.C. § 103(a) - the Tateishi and Shirasaki references

Claim 8 is rejected under 35 U.S.C. § 103(a) as being obvious over Tateishi et al. (Journal of Cerebral Blood Flow & Metabolism, June 2002, vol. 22, no. 6, pp. 723-734) as applied to claims 1, 6, 7, 9-16, 29 and 35 above in view of Shirasaki et al. (US 5,837,706).

The Examiner states one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine use an infusion bag administration in the method of Tateishi et al. because Shirasaki et al. teach that cerebrovascular disorders such as cerebral infarction is preferably treated through the intravenous drip infusion administration route.

In view of Applicant's arguments made above, Tateishi fails to teach, suggest or motivate one of ordinary skill in the art to practice Applicants' invention and Shirasaki fails to the remedy the deficiencies of the Tateishi reference.

Applicant's invention is not obvious in view of the references cited by the Examiner

Applicants assert that, contrary to the arguments made by the Examiner,

(1) the Tateishi reference fails to teach, suggest or motivate a person of ordinary skill to administer a dose of between 2 - 12 mg/kg/ h of (2R)-2-propyloctanoic acid for the treatment of cerebral ischemia without adverse side effects as required by Applicant's invention.

(2) the efficacy and tolerance of high dose (2R)-2-propyloctanoic acid in humans is unpredictable,

(3) the Tateishi reference fails to teach, suggest or motivate a person of ordinary skill to administer high dose (2R)-2-propyloctanoic acid for period of time lasting 3 hours or less, and

Hence, Applicants contend the teachings of Tateishi combined with the knowledge in the art at the time of filing of the Application would not motivate one of ordinary skill to test a high dose of (2R)-2-propyloctanoic acid for the treatment of stroke in humans. Moreover, a person of

ordinary skill would not have been inclined to try Applicant's high dose regimen of (2R)-2-propyloctanoic acid because there was no reasonable expectation of success in treating cerebral ischemia at such doses without adverse side effects.

Applicants therefore affirm the claimed invention is not obvious in view of the Tateishi reference or in combination with Shirasaki and respectfully request withdrawal of the rejection of the claimed invention under 35 U.S.C. § 103(a).

CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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